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EDITORIAL

Guidelines to improve urticarial care and the remaining research gaps

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Chronic urticaria is a common disorder that affects everyone's quality of life and significantly impact the health economy. Lately, publications of urticaria-related articles have gone up to 250 annually. Recent practice guidelines both from Europe and the United States have been updated to help improve the management of patients with urticaria.[1-3] Whether there is a need for having region- or country-specific guidelines to address some specific issues is not known.[4,5] In principle, the evidence-based recommendations will be the same as highlighted in table 1. There are only 2 types of treatment that can be strongly recommended with high level of evidences,based on more than 1 large double-blinded, randomized-controlled trials (RDBPCT): the use of second-generation antihistamines as first-line therapy,[6-8] or omalizumab as its alternative therapy.[9] Only these 2 therapeutic options are licensed. The recommendation of up to 4-fold increase of second-generation antihistamines is actually based on a single well-designed, but small sample size, double-blinded,randomized-controlled trial (RDBPCT).[10] Non-pharmacotherapy, although did not have well-controlled evidence support, is important and should always be emphasized during patient education to minimize dryness of the skin and to minimize aggravating skin hypersensitivity. When developing a guideline for managing urticaria, the regional and country specific issues may be more relevant in case of etiology, nature of urticarial/angioedeme and different response rate to a particular treatment.

Only few studies have provided complete urticaria controlled rates

It is worth mentioning that when a conclusion from a RDBPCT showed a treatment option had a better urticarial clinical control than the placebo, it was primarily based on whether there was a significant symptom score improvement at the primary endpoint. From the patient's perspective, however, the proportion of total long-term remission is the ultimate goal which is unlikely to be assessed in most studies.

It should be noted that in most randomized-controlled studies that used second-generation antihistamines as its first-line of treatment did not report the complete urticarial control rates.[6-8] On the other hand, even though with small sample size, an antihistamine-dose increasing study provided more information for patients. For example, those treated with levocetirizine at the licensing dose (5 mg) had complete control up to 20%, and for those "non-responders", 42% could control their urticaria when the dose was doubled or quadrupled. In contrast, in a recent RCT of Omalizumab, only approximately one-third of the patients showed a complete urticarial control (i.e., 35.8% vs 8.8% in placebo group; $p<0.0001$).[9]

Unlike urticaria, angioedema is clinically more difficult to treat and often responds less well to antihistamine. However, a very recent RDBPCT study showed that omalizumab was efficacious in patients unresponsive to high doses of antihistamines. But after 24 weeks of treatment, the symptoms returned in majority of the patients, although with median time to first recurrence of angioedema was much longer than those in the placebo group (57–63 days with vs <5 days).[11]

More research needs to be done

Despite all of these studies, yet there are several knowledge gaps that warrant for further investigation, including durability of the response to omalizumab and its optimal duration of treatment are not known. There are some many unanswered questions. For instance, how to treat patients who have failed both high dose antihistamine and omalizumab? What is/are the pathogenesis of urticaria in this population? Will there be any potential markers to predict responders to omalizumab? What are the nature of urticaria and treatment responses between different regions or ethnicities? What is the proper treatment for chronic inducible urticaria (CiU)? As you can see here, there are so many unanswered questions which require further investigation.

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Summary of Chronic Urticaria Clinical Practice Guidelines

***Step 1* : Recommended first-line treatment**

1. **Treating or avoiding known etiology**
2. **Non-pharmacotherapy** to minimize hyper-responsive skin: *prevention skin from drying, avoidance of hot shower, scrubbing, and excessive sun exposure*
3. **Non-sedating antihistamines:** 2-4 weeks

***Step 2* : When failed from step 1**

1. **Increase the dose** of non-sedating antihistamine up to 4-fold x 4 weeks
2. **Emphasis on non-pharmacotherapy**

***Step 3* : When failed step 2**

1. **Anti-IgE antibody (Omalizumab®)** - if affordable or accessible *(strong evidences)*
2. **Other alternatives** *(weaker evidences)*:
   - Leukotriene receptor antagonists
   - H2 receptor blockers, others

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